amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1), of the ECRTP/DEP-1 ectodomain.

Please replace claim 11 with the following amended claim:

11. The antibody of claim 8, wherein the humanized antibody comprises monoclonal antibody ECRTPAb-1, having a molecular weight of about 150 kDa and which selectively binds to an ectodomain of the ECRTP/DEP-1.

REMARKS

I. Status Summary

Claims 2-8 and 10-55 are pending in the present U.S. patent application. Claims 15-44 have been withdrawn from consideration. Claims 2-8, 10-14, and 45-55 are pending and have been examined.

Claims 2, 3, 5, 10, and 11 have been amended to replace "preferentially" with "selectively". Support for the amendments can be found throughout the specification, for example, on page 48, lines 1-8, and on page 49, lines 12-21. Additional support can be found in the Examples, particularly in Example 1 on page 82, line 12, through page 92, line 9, Example 2 on pages 98, line 15, through page 99, line 13, and Example 4 on page 110, lines 7-22.

Claims 3 and 10 have been amended to clarify that the phrase "analog sequence" refers to a sequence of an analog.

Claim 11 has been amended to depend from claim 8 instead of claim 9, which was cancelled in a prior amendment. Claim 9 had depended from claim 8. The above amendments do not introduce any new matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**". Deletions are bracketed and additions are underlined and in boldface type. Reconsideration of the application as amended and based on the arguments set forth herein below is respectfully requested.

II. Purpose of Amendment to Example 4

The amendment to the specification at Example 4 is being offered solely to correct a typographical error that appears on page 110 of the application as originally filed. No new matter has been added by this amendment. The amendment corrects the amino acid sequence identified in Example 4 as the amino acid sequence of peptide #41. Support for the amendment can be found throughout the specification, for example, at pages 18, lines 6-7. Additionally, Amendment A of the instant application (filed May 28, 2002) identified both the n-QSRDTEVL-c sequence (correct) and the n-QSRNDEVL-c sequence (incorrect) as SEQ ID NO:1. The instant amendment serves to clarify that SEQ ID NO:1 should refer to the sequence n-QSRDTEVL-c only.

III. Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 2-4, 8-11, and dependent claims thereof (which includes pending claims 5-7, 12-14, and 45-55) under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the term "preferentially", has been maintained from the prior Official Action. The United States Patent and Trademark Office (hereinafter the "Patent Office") contends that the term preferentially "does not specifically localize the binding epitope of the antibody", and as a result "one of skill in the art would find it hard to pinpoint the exact location within the ectodomain of this protein to find the exact epitope." Official Action at page 3. The Patent Office further contends that antibodies such as polyclonals "that recognized ectodomains and cytoplasmic domains would read on the term 'preferentially', because polyclonals can mostly comprise antibodies that bind to the ectodomain and some that bind cytoplasmically". Id.

The rejection of claims 3, 10, and dependent claims thereof (which includes pending claim 54) under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of the term "analog sequence", has been maintained from the prior Official Action. The Patent Office contends that "[b]ecause the term can encompass a multitude of possible 'analogs', one of skill in the art could not possibly know or understand the meaning or the exact 'analog' to which the instant invention refers". Id. After careful consideration of the rejections, applicants respectfully traverse the rejections and submit the following comments.

III.A. The Term "Preferentially"

The Patent Office first contends that claims 2-4, 8-11, and dependent claims thereof are indefinite because the metes and bounds of the term "preferentially" are not clear. Applicants respectfully traverse the rejection and submit the following comments.

Claims 2, 3, 5, 10, and 11 have been amended for clarity to insert "selectively" in place of "preferentially". Support and guidance for this amendment can be found throughout the specification, including, for example, on page 48, lines 1-8 and on page 49, lines 12-21. Additional support can be found in the Examples, particularly in Example 1 on page 82, line 12, through page 92, line 9, Example 2 on pages 98, line 15, through page 99, line 13, and Example 4 on page 110, lines 7-22. Applicants wish to point out that claim 9 was cancelled in a prior amendment, so the rejection under 35 U.S.C. § 112, second paragraph, has been rendered moot as to this claim. Applicants submit that in light of the amendments, claims 2, 3, 5, 10, and 11, and all dependent claims thereof, including 4, 6-8, 12-14, and 45-55, are definite and respectfully request that the rejection of claims 2-4, 8, 10, 11, and dependent claims thereof under 35 U.S.C. § 112, second paragraph, be withdrawn. Applicants further submit that claims 2-8, 10-14, and 45-55 are in condition for allowance and respectfully solicit the same.

III.B. The Term "Analog Sequence"

Next, the Patent Office contends that claims 3, 10, and dependent claims thereof (which includes pending claim 54) are indefinite in the recitation of the term

"analog sequence". Applicants respectfully traverse the rejection and submit the following comments.

Claims 3 and 10 have been amended to clarify that "analog sequence" refers to the sequence of an analog. "Analog", as defined in the specification,

> includes any polypeptide having an amino acid residue sequence substantially identical to a sequence of the natural ligand of the ECRTP/DEP-1 in which one or more residues have been conservatively substituted with a functionally similar residue and which displays the ECRTP/DEP-1 modulator activity as described herein. Examples of conservative substitutions include the substitution of one non-polar (hydrophobic) residue such as isoleucine, valine, leucine or methionine for another; the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, between glycine and serine; the substitution of one basic residue such as lysine, arginine or histidine for another; or the substitution of one acidic residue, such as aspartic acid or glutamic acid for another.

Specification at page 36.

The paragraphs following the definition of the term "analog" (for example, page 36, line 22 through page 38, line 22) further clarify the meaning and usage of the term. As the claims are to be read in the light of the specification, applicants submit that the specification makes the meaning of the term "analog" as used in the amended claims clear and thus the term is not ambiguous. Applicants therefore respectfully request that the rejection of claims 3 and 10 under 35 U.S.C. § 112, second paragraph be withdrawn. Applicants further submit that claims 3 and 10 are in condition for allowance and respectfully solicit the same.

IV. Claim Rejection under 35 U.S.C. § 102(b)

Claims 2, 4, 8, 14, 45, and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Tonks *et al.* (WO 95/30008, hereinafter "Tonks"). The Patent Office asserts that these claims are drawn to an antibody that binds to the ectodomain of ECRTP/DEP-1 and has activity in modulating angiogenesis. The Patent Office contends:

> Tonks *et al* teach an antibody that binds to DEP-1, which appears to be the same protein and has the same function as the protein described in the instant application. This disclosure of Tonks *et al* also teaches that the antibody can be used in a pharmaceutical capacity for the modulation of biological activities of DEP-1 protein. Since the antibody of Tonks *et al* is to be used in an in vivo capacity, presumably, the antibody will bind to the ectodomain of DEP-1 to modulate its activity. Furthermore, in the absence of any evidence to the contrary, since the ECRTP/DEP-1 protein has been implicated in angiogenesis, the antibody disclosed by Tonks *et al* may also have activity in modulating angiogenesis.

Official Action at page 4.

After careful consideration of this rejection, applicants respectfully traverse the rejection and submit the following comments.

It is well settled that for a cited reference to qualify as prior art under 35 U.S.C. § 102, each element of the claimed invention must be disclosed within the reference. "It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986). Upon careful consideration and review of Tonks, applicants submit that the disclosure of Tonks does not disclose each and every element of the present invention. Specifically, the disclosure of Tonks does not disclose antibodies that bind to the ectodomain of ECRTP/DEP-1. Tonks discloses

antibodies made against two peptides. These peptides are described in the reference as "corresponding to amino acid residues 1297 through 1315 and residues 1321 through 1334" in SEQ ID NO: 2 of the PCT application. Tonks at page 18. According to the specification of the instant application, these residues fall outside of the ectodomain, which corresponds to amino acids 1-351 (see page 42, lines 6-7). As such, the antibodies disclosed in Tonks do not bind to the ectodomain. Claim 2 of the instant application recites an antibody that selectively binds an ectodomain of ECRTP/DEP-1. Since Tonks does not disclose an antibody that specifically binds to the ectodomain if ECRTP/DEP-1, the cited reference does not disclose each and every element of the present invention.

Claims 4, 8, 14, 45, and 46 depend directly or indirectly from claim 2, and therefore include this element. In addition, several of these claims recite additional elements that are not disclosed in Tonks. For example, claim 8 adds the limitation that the antibody of claim 2 is a humanized antibody. Similarly, claims 45 and 46 recite an antibody of claim 2 or claim 8, respectively, which has activity in modulating angiogenesis. As discussed in more detail below, Tonks does not disclose these additional elements, either explicitly or inherently. Accordingly, applicants respectfully submit that Tonks does not disclose each and every element recited in claims 4, 14, 45 and 46.

As discussed above, Tonks does not explicitly disclose an antibody that binds to the ectodomain of ECRTP/DEP-1. The Patent Office nonetheless contends that "[s]ince the antibody of Tonks et al is to be used in an in vivo capacity, presumably, the antibody will bind to the ectodomain of DEP-1 to modulate its activity." Official Action

at page 4. It appears that the Patent Office is asserting that the antibody disclosed in Tonks inherently might bind to the ectodomain of ECRTP/DEP-1 on the basis of its purported use *in vivo*. However, the Court of Appeals for the Federal Circuit (C.A.F.C.) has indicated that "an inherent limitation is one that is necessarily present; invalidation based on inherency is not established by 'probabilities or possibilities'." Scaltech, Inc. v. Retec/Tetra, LLC., 178 F.3d 1378, 1384, 51 USPQ2d 1055, 1059 (Fed. Cir. 1999). Furthermore, the C.A.F.C. stated, "the mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency". Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Applicants respectfully submit that, in view of the Scaltech and Continental Can cases, the Patent Office has impermissibly inferred that an element of the instant invention is disclosed by the Tonks reference. Since the antibody in Tonks cannot be said to inevitably bind to the ectodomain of ECRTP/DEP-1, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) based on the Tonks reference be withdrawn, and that the claims be allowed at this time.

The Patent Office also contends that Tonks teaches an antibody that can be used "in a pharmaceutical capacity for the modulation of biological activities of DEP-1 protein", and furthermore that "since the ECRTP/DEP-1 protein has been implicated in angiogenesis, the antibody disclosed by Tonks et al may also have activity in modulating angiogenesis". Official Action at page 4. Applicants respectfully submit that these presumptions also fail to establish a *prima facie* case of anticipation. Applicants initially note that examination of the Tonks application demonstrates that it refers to anti-DEP-1 antibodies as binding molecules, which are defined as "useful for

purification of Type III density enhanced phosphatase [DEP] polypeptides...and for identifying cell types which express the polypeptide. Binding molecules are also useful for modulating...the *in* vivo binding and/or signal transduction activities of Type III [DEPs]". Tonks at pages 8-9. This passing reference to binding molecules generally as being "useful for modulating...the *in vivo* binding and/or signal transduction activities" of proteins to which they bind does not suffice to anticipate the antibodies of the present invention, particularly in view of the treatment of inherency in the Scaltech and Continental Can cases discussed above.

In summary, then, applicants respectfully submit that the Patent Office has failed to establish a prima facie case of anticipation based on the Tonks reference. Accordingly, applicants respectfully request that the rejection of claims 2, 4, 8, 14, 45, and 46 under 35 U.S.C. § 102(b) be withdrawn and the claims be allowed at this time.

V. Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 2-4, 6, 8, 10, 12-14, and 45-55 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Official Action at pages 4-5. The Patent Office contends that the written description of the application as filed sets forth only an antibody that binds to ECRTP/DEP-1, and that therefore the written description does not adequately describe to one of skill in the art fragments or derivatives of the antibody that bind to ECRTP/DEP-1. Further, the Patent Office contends:

> With the exception of the antibody that binds to ECRTP/DEP-1, the skilled artisan cannot envision the detailed structure of the encompassed fragments or derivatives and therefore conception is not achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it or preparing such fragments or derivatives. The amino acid sequence itself is required.

Official Action at page 4.

While the Patent Office acknowledges that support for fragments and derivatives is provided on pages 35-36 of the specification, the Patent Office contends, "no disclosure, beyond the mere mention of fragments or derivatives is made in the specification". Official Action at page 6. After careful consideration of this rejection, applicants respectfully traverse the rejection and submit the following comments.

Applicants initially note that as a matter of Patent Office practice, the burden rests upon the Patent Office to establish a *prima facie* case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the invention described and claimed in applicants' patent application. *See* Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (hereinafter "The Guidelines"), 66 Fed. Reg. at 1105. This includes "the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims". Id. Additionally, The Guidelines state that there is a "strong presumption that an adequate written description of the claimed invention is present in the specification as filed". Id., citing In re Wertheim, 541 F.2d 257, 262 (CCPA 1976). Furthermore, the Patent Office must establish "by a preponderance of the evidence why a person skilled in the

art would not recognize in an applicant's disclosure a description of the invention defined in the claims". Id. at 1107, citing Wertheim, at page 263.

The Patent Office contends that the specification of the present U.S. patent application does not show that applicants were in possession of the claimed invention. However, no specific scientific or other factual basis in support of this contention has been presented in the Official Action. Rather, the Patent Office has offered only a series of conclusory statements, contending generally that the specification of the present patent application does not adequately describe to one of skill in the art "fragments or derivatives of the antibody that binds to ECRTP/DEP-1". Official Action at page 5. According to The Guidelines, "a general allegation of 'unpredictability in the art' is not a sufficient reason to support a rejection for lack of adequate written description". The Guidelines at page 1107. Indeed, 35 U.S.C. §112, first paragraph requires no more than a disclosure sufficient to convey to one of ordinary skill in the art that applicants were in possession of the invention commensurate with the scope of the claims (*see* The Guidelines at page 1105, citing Wang Labs. v. Toshiba Corp., 993 F.2d 858, 865 (Fed. Cir. 1993)), and this requirement has clearly been met. As a result, applicants respectfully submit that a *prima facie* case under 35 U.S.C. §112, first paragraph, has not been made out. Accordingly, 2-4, 6, 8, 10, 12-14, and 45-55 are believed to be in compliance with 35 U.S.C. §112, first paragraph. Withdrawal of this rejection of claims 2-4, 6, 8, 10, 12-14, and 45-55 is respectfully requested.

However, assuming *arguendo* that the Patent Office has made a *prima facie* case of a failure to comply with 35 U.S.C. §112, first paragraph, applicants respectfully submit the following.

The Patent Office's primary contention in support of the rejection under 35 U.S.C. §112, first paragraph, appears to be that the specification does not provide adequate written description for the broad class of *any* and *all* fragments or derivatives of the antibody that binds to ECRTP/DEP-1. The Patent Office contends that the holdings of Fiers v. Revel, Amgen v. Chugai, and Regents v. Eli Lilly compel the production of the exact amino acid sequences for all fragments or derivatives now claimed. The Patent Office states: "With the exception of the antibody that binds to ECRTP/DEP-1, the skilled artisan cannot envision the detailed structure of the encompassed fragments or derivatives and therefore conception is not achieved until reduction to practice has occurred." Furthermore, the Patent Office asserts, "although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins". Official Action at page 5. Applicants respectfully note that, contrary to the Patent Office's assertions, this line of cases is inapplicable to the issue of the current rejection, and that the holdings in these cases involved issues and facts that are not "clearly applicable to the claimed proteins".

In Amgen v. Chugai, the C.A.F.C. held that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated" (emphasis added). Amgen v. Chugai involved claims to the human erythropoietin nucleotide sequence based upon the peptide sequence of the human erythropoietin protein. Due to the redundancy of the genetic code, the C.A.F.C. held that possession of the polypeptide sequence did not result in possession of the nucleotide sequence. In Fiers v. Revel,

the C.A.F.C. held that conception of a DNA sequence coding for a particular protein does not occur upon conception solely of a method of obtaining it. Relying on Amgen v. Chugai, the C.A.F.C. reiterated that conception of a DNA sequence of a product having a particular biological activity or function is not complete until one can define the DNA sequence by other than the particular biological activity or function of the encoded gene. And finally, in Regents v. Eli Lilly, the C.A.F.C. held that disclosure of a rat cDNA for the insulin gene plus a method for isolating the human insulin cDNA based upon the rat sequence was insufficient to describe the human cDNA sequence.

These cases are inapplicable to the current invention because their holdings are based upon the unpredictability of the art of cloning genes and cDNAs, an unpredictability that is absent from the antibody art of the present invention. The cited cases involve situations where the applicants tried to show conception of a specific human cDNA sequence based upon general methods for cloning a cDNA sequence in conjunction with knowledge of, 1) a protein sequence (Amgen); 2) a functional activity (Fiers); or 3) a rat cDNA sequence (Eli Lilly). In each case, the C.A.F.C. pointed out that the specific nucleotide sequence could not be envisioned until a reduction to practice had occurred because a specific DNA sequence cannot be predicted from a protein sequence, a functional description, or a homologous gene from another species.

This is not the situation presented by the present application. According to Example 16 of the Synopsis of Application of Written Description Guidelines (available from the Patent Office website), the antibody art as a "well-developed art". With regard to fragments or derivatives of antibodies, the skilled artisan can immediately

envision the detailed structures of the encompassed fragments or derivatives because standard techniques that are well known in the art are used to produce the various fragments and derivatives of the present invention. These standard methods, as described above and in the specification, produce the various fragments and derivatives that make up embodiments of the present invention. As these techniques and the fragments they produce are well understood in a "well developed art", applicants respectfully submit that one of skill in the art would immediately understand that applicants were in possession of the antibodies, fragments, and derivatives of the present invention.

Amended claims 2, 3, 5, 10, and 11 recite an antibody or a fragment or derivative thereof that selectively binds an ectodomain of an ECRTP/DEP-1. Support for this amendment can be found throughout the specification, as noted herein above. Applicants further note that Examples 2 and 5 employ one such fragment, the Fab fragment of monoclonal antibody ECRTPAb-1, and Figures 8-10 and 13 present data involving use of the Fab fragment of this antibody. In addition, other relevant fragments are described in the application, including single chain antibodies (pages 48-49) and two-chain and single chain F(v) fragments (pages 49-50). And finally, fragments such as the Fab' and $F(ab')_2$ fragments that are recited in claims 47-52 are well known in the art to be the products of standard manipulations of antibodies. For example, an $F(ab')_2$ fragment is produced by treating an antibody with pepsin. An Fab' fragment results from reducing the disulfide bridges of an $F(ab')_2$ fragment. *See, e.g.*, U.S. Patent No. 6,455,683 to Yang *et al.*; U.S. Patent No. 6,455,292 to Shu *et al.* Additionally, an enzymatic cleavage using papain produces two monovalent Fab

fragments and an Fc fragment directly. These methods are described, for example, in U.S. Pat. Nos. 4,036,945 to Haber and 4,331,647 to Goldenberg, and references contained therein. *See also* Edelman *et al.*, Methods In Enzymology, Vol. 1, page 422 (Academic Press 1967); Harlow and Lane, Antibodies – A Laboratory Manual (Cold Spring Harbor Laboratory 1988). As such, in the well-developed art of antibodies, a skilled artisan would immediately understand that possession of an antibody also encompasses possession of these fragments and derivatives.

Thus, applicants submit that claims 2, 3, 5, 10, and 11 recite subject matter described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Indeed, the C.A.F.C. has held: "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met". In re Alton, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996). Applicants submit that claims 2, 3, 5, 10, and 11 recite an antibody or a fragment or derivative of the antibody that selectively binds an ectodomain of an ECRTP/DEP-1. Additionally, claim 2 recites a characteristic of the antibody or fragment or derivative thereof, namely selective binding to an ectodomain of an ECRTP/DEP-1. The antibody, fragment, or derivative thereof and the recited characteristic are both supported in the specification. Applicants submit that one of ordinary skill in the art would recognize that the inventor was in possession of the invention, and that the written description requirement of 35 U.S.C. §112, first paragraph, is satisfied. Accordingly, applicants respectfully request

that the rejection of claims 2-4, 6, 8, 10, 12-14, and 45-55 under 35 U.S.C. §112, first paragraph, be withdrawn. Allowance of claims 2-8, 10-14, and 45-55 is also respectfully requested.

CONCLUSIONS

In light of the above Amendment and Remarks it is respectfully submitted that the present application is now in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

DEPOSIT ACCOUNT

The Assistant Commissioner is hereby authorized to charge any deficiencies or credit any overpayments associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS & WILSON, P.A.

Date: 01/06/2003 By: _____

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1242/12/2 CIP AAT/CPP/ptw

Attachments:
Version with Markings to Show Changes Made

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Daniel et al. Group Art Unit: 1642

Serial No.: **09/516,728** Examiner: Yaen, C.

Filed: March 1, 2000 Atty Docket No.: 1242/12/2/CIP

For: MODULATION OF ENDOTHELIAL CELL SURFACE RECEPTOR ACTIVITY IN THE REGULATION OF ANGIOGENESIS

* * * * * * * * * * * * *

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Deleted text is enclosed in brackets ([ ]). Text to be added is underlined and in bold typeface.

IN THE SPECIFICATION:

The paragraph beginning at page 1, line 4, has been amended as follows:

This application is a continuation-in-part of co-pending U.S. Patent application serial number 09/152,160, filed September 10, 1998, **now U.S. Patent No. 6,248,327,** herein incorporated by reference in its entirety.

The paragraph beginning at page 110, line 7, has been amended as follows:

EXAMPLE 4

Identification of Binding Epitope for ECRTPAb-1

A series of 96 eight to nine amino acid peptides was generated. The eight to nine amino acid peptides span in overlapping epitopes the 351 amino acid sequence

against which ECRTPAb-1 was derived was generated. These peptides were generated and immobilized in a defined array on the surface of a membrane that was probed with ECRTPAb-1. Binding of ECRTPAb-1 to peptide #41 in the array was identified using a peroxidase-conjugated anti-mouse IgG second antibody, by chemiluminescence autoradiography (Figure 12). The sequence of this peptide derived from the array is [n-QSRNDEVL-c] **n-QSRDTEVL-c** (SEQ ID NO:1). The 8-amino acid epitope represents the target sequence within the ECRTP ectodomain against which functional ECRTP agonists and antagonists interact, based on biological activities of ECRTPAb-1. Antibodies, including humanized antibodies, and other peptides with high affinity for this defined amino acid sequence have biological activities comparable to those demonstrated herein using ECRTPAb-1.

Claim 2 has been amended as follows:

2. An antibody**, or a fragment or derivative thereof,** that [preferentially] **selectively** binds an ectodomain of **an** [the] ECRTP/DEP-1[, or a fragment or derivative of the antibody].

Claim 3 has been amended as follows:

3. The antibody of claim 2, which [preferentially] **selectively** binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1), or an **analog of the** eight amino acid epitope having [an analog sequence of] the sequence QSRDTEVL (SEQ ID NO: 1)[,] of the ECRTP/DEP-1 ectodomain.

Claim 5 has been amended as follows:

5. The antibody of claim 4, which is monoclonal antibody ECRTPAb-1, having a molecular weight of about 150 kDa and which [preferentially] **selectively** binds to an ectodomain of the ECRTP/DEP-1.

Claim 10 has been amended as follows:

10. The antibody of claim [9] **8**, which [preferentially] **selectively** binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1) or an **analog of an** eight amino acid epitope having [an analog sequence of] the sequence QSRDTEVL (SEQ ID NO: 1), of the ECRTP/DEP-1 ectodomain.

Claim 11 has been amended as follows:

11. The antibody of claim 8, wherein the humanized antibody comprises monoclonal antibody ECRTPAb-1, having a molecular weight of about 150 kDa and which [preferentially] **selectively** binds to an ectodomain of the ECRTP/DEP-1.

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IN THE SPECIFICATION:

The sentence beginning on page 18, line 1, has been amended as follows:

-- Figure 12 is an autoradiograph showing that ECRTPAb-1 binds peptide sequence QSRDTEVL (SEQ ID NO: 1) of ECRTP/DEP-1 ectodomain. --

The sentence beginning on page 18, line 7, has been amended as follows:

-- A single peptide sequence (#41) in the series represents amino acid residues in n-QSRDTEVL-c (SEQ ID NO: 1). --

The sentence beginning on page 42, line 7, has been amended as follows:

-- More preferably, an antibody of the present invention preferentially binds an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein, of the ECRTP/DEP-1 ectodomain. --

The sentence beginning on page 46, line 20, has been amended as follows:

-- A preferred target molecule comprises a polypeptide fragment of the ECRTP/DEP-1 ectodomain includes an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having

an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein. --

The sentence beginning on page 47, line 8, has been amended as follows:

-- A preferred target molecule comprises a polypeptide fragment of the ECRTP/DEP-1 ectodomain includes an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein. --

The sentence beginning on page 48, line 4, has been amended as follows:

-- Preferably, an antibody of the present invention preferentially binds an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein, of the ECRTP/DEP-1 ectodomain. –

The sentence beginning on page 49, line 17, has been amended as follows:

-- Preferably, an antibody of the present invention preferentially binds an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein, of the ECRTP/DEP-1 ectodomain. --

The sentence beginning on page 51, line 12, has been amended as follows:

-- In one embodiment, a modulator of the present invention interacts with an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1) of the ECRTP/DEP-1 ectodomain. –

The sentence beginning on page 58, line 11, has been amended as follows:

-- Preferably, the ECRTP/DEP-1 ectodomain fragment comprises an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein. --

The sentence beginning on page 59, line 4, has been amended as follows:

-- The kit comprises a binding agent comprising a polypeptide fragment of the ECRTP/DEP-1 ectodomain that comprises an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein, contained in a first container. --

The sentence beginning on page 61, line 10, has been amended as follows:

-- Additionally, a modulator of the present invention can be screened for interaction with an eight amino acid epitope having the sequence n-QSRDTEVL-c (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the

sequence n-QSRDTEVL-c (SEQ ID NO: 1), the term "analog" as defined herein, of the ECRTP/DEP-1 ectodomain. --

The sentence on page 110, line 16, has been amended as follows:

-- The sequence of this peptide derived from the array is n-QSRNDEVL-c (SEQ ID NO: 1). --

The sentence beginning on page 78, line 7, has been amended as follows:

-- Finally, in the case of methotrexate or aminopterin, attachment is achieved through a peptide spacer such as L-Leu-L-Ala-L-Leu-L-Ala (SEQ ID NO: 2), between the γ-carboxyl group of the drug and an amino acid of the antibody. --

IN THE CLAIMS:

Please cancel claims 1 and 9 without prejudice.

Please amend claims 2-4, 6, 8, 10, 12, 13 and 14 as follows:

2. (Once Amended) An [The] antibody [of claim 1, which] that preferentially binds an ectodomain of the ECRTP/DEP-1, or a fragment or derivative of the antibody.

3. (Once Amended) The antibody of claim 2, which preferentially binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence QSRDTEVL (SEQ ID NO: 1), of the ECRTP/DEP-1 ectodomain.

4. (Once Amended) The antibody of claim 2, [1] which is a monoclonal antibody or a fragment or derivative thereof.

6. (Once Amended) The antibody of claim 4, further characterized as having the specificity [immunoreaction characteristics] of a monoclonal antibody produced by a hybridoma cell line having ATCC accession number HB12570.

8. (Once Amended) The antibody of claim 2 [1], wherein the antibody is humanized.

10. (Once Amended) The antibody of claim 9, which preferentially binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1), or an eight amino acid epitope having an analog sequence of the sequence QSRDTEVL (SEQ ID NO: 1), of the ECRTP/DEP-1 ectodomain.

12. (Once Amended) The antibody of claim 8, wherein the humanized antibody is further characterized as having the specificity [immunoreaction characteristics] of a monoclonal antibody produced by a hybridoma cell line having ATCC accession number HB12570.

13. (Once Amended) The antibody of claim 12, where the [monoclonal] humanized antibody is a monoclonal antibody produced by a hybridoma cell line having ATCC accession number HB12570.

14. (Once Amended) The antibody of claim 2 [1], in a pharmaceutically acceptable diluent or excipient.

Please add the following new claim:

45. (New) The antibody of claim 2, which has activity in the modulation of angiogenesis.

46. (New) The antibody of claim 8, which has activity in the modulation of angiogenesis.

47. (New) The antibody of claim 2, wherein the antibody fragment is selected from the group consisting of an Fab fragment, an Fab´ fragment, an F(ab´)2 fragment and an F(v) fragment.

48. (New) The antibody of claim 47, wherein the F(v) fragment is an scFv fragment.

49. (New) The antibody of claim 4, wherein the antibody fragment is selected from the group consisting of an Fab fragment, an Fab´ fragment, an F(ab´)2 fragment and an F(v) fragment.

50. (New) The antibody of claim 49, wherein the F(v) fragment is an scFv fragment.

51. (New) The antibody of claim 8, wherein the antibody fragment is selected from the group consisting of an Fab fragment, an Fab´fragment, an F(ab´)2 fragment and an F(v) fragment.

52. (New) The antibody of claim 51, wherein the F(v) fragment is an scFv fragment.

53. (New) The antibody of claim 3, which binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1).

54. (New) The antibody of claim 10, which binds an eight amino acid epitope having the sequence QSRDTEVL (SEQ ID NO: 1).

55. (New) An antibody having the specificity of an antibody produced by the hybridoma cell line having ATCC accession number HB12570.